

CLAIMS

1. A hyperbranched amidoamine polymer comprising [A] a first structural repeating unit having a connectivity of three consisting of a nitrogen core linked to a first amidoamine unit, a second amidoamine unit and a third amidoamine unit, [B] a second structural repeating unit having a connectivity of two consisting of a nitrogen core linked to a first amidoamine unit and a second amidoamine unit and [C] terminal units of which a major portion comprises amine groups or a functional derivative thereof, and a minor portion comprises carboxylic acid or related groups or a functional derivative thereof.

2. A polymer according to claim 1, wherein the ratio of structural repeating units having a connectivity of three to structural repeating units having a connectivity of two and terminal units is in the range of 1:10:20 to 1:2:2.5.

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3. A hyperbranched amidoamine polymer whose molecules are characterised by a nitrogen core linked to:

a first irregularly branched amidoamine unit terminating in an amine group or a functional derivative thereof:

a second irregularly branched amidoamine unit terminating in a amine group or a functional derivative thereof: and

a third irregularly branched amidoamine unit terminating in a carboxylic acid or related group or a functional derivative thereof.

4. A polymer according to any of claims 1 to 3, having a theoretical degree of branching of up to 50%.

5. A polymer according to claim 4, having a theoretical
5 degree of branching of up to 67%, up to 75%, or up to 80%.

6. A polymer according to any one of claims 3 to 5,
wherein each of the first, second and third irregularly
10 branched amidoamine units includes consecutive,
irregularly branched aminoamine moieties each having two
or more amido groups.

7. A polymer according to any one of claims 3 to 6,
15 wherein the amine group or functional derivative thereof
in which the first and second irregularly branched
amidoamine unit terminates is a primary amine group or a
functional derivative thereof.

20 8. A polymer according to claim 7, in which the
functional derivative is a secondary, tertiary, or
quaternary amine group, an aromatic or aliphatic amide
group, a cyano group, a sulphur containing group, a
cross-linking group, an anilino group or an acyclic
25 polynitrogen group.

9. A polymer according to claim 8, in which the
functional derivative is an amine group substituted with
one, two or three C₁₋₆ - alkyl groups, or an amine group
30 substituted with an N, N - substituted amidoamine group.

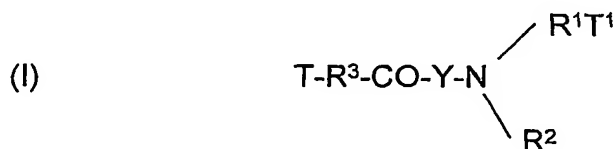
10. A polymer according to claim 9, in which the
functional derivative is a quaternary amine group.

11. A polymer according to any one of the preceding claims, wherein the related group of the carboxylic acid is selected from the group consisting of a salt, ester, anhydride, acid halide, acyl, amide, imide, nitrile, aldehyde and a hydrazide group.

12. A polymer according to any one of the preceding claims, wherein the functional derivative of the carboxylic acid is a carboxyl protecting or blocking group or a group chosen to suit the desired function of the polymer.

13. A polymer according to any one of claims 3 to 12, wherein the third irregularly branched amidoamine unit terminates in a carboxylic acid group or a functional derivative thereof.

14. A hyperbranched amidoamine polymer of formula I:



wherein:

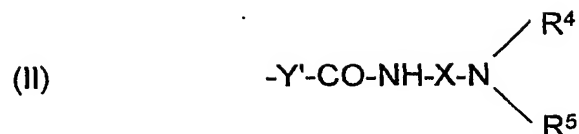
Y is a divalent bridging group;

T together with a terminal CO group of R^3 to which it is bound is a carboxylic acid or related group or a functional derivative thereof;

T^1 together with a terminal nitrogen atom of R^1 to which it is bound is an amine group or a functional derivative thereof;

R^1 is an amidoamine unit of formula II;

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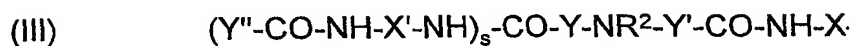
wherein:

5 each of X and Y' which may be the same or different
is a divalent bridging group;

R⁴ is either

(a) n consecutive amidoamine moieties of formula
III;

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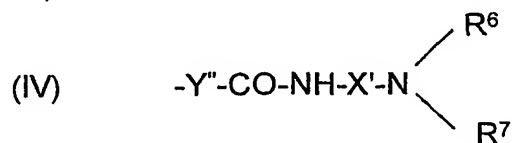
wherein:

s is 0 or 1;

15 n is a number greater than 0;

each of X' and Y'' which may be the same or different is a
divalent bridging group, or

(b) an amidoamine unit of formula IV;



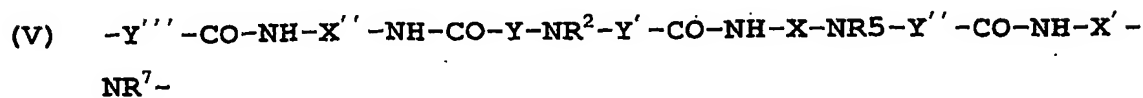
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wherein:

R⁶ is either

(a) m consecutive amidoamine moieties of formula V:

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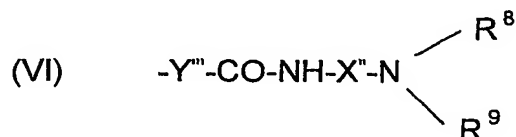


wherein:

m is a number greater than 0;

each of X'' and Y''' which may be the same or different is a divalent bridging group or

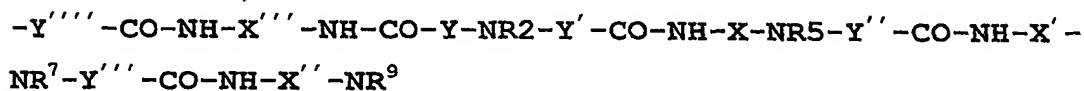
- 5 (b) an amidoamine unit of formula VI:



wherein:

R⁸ is x consecutive amidoamine moieties of formula VII:

10



(VII)

wherein:

15

X is a number greater than 0;

Each of X''' and Y'''' which may be the same or different is a divalent bridging group; and

20

R⁹ is R¹ T¹ or is a group as hereinbefore defined for R⁸ T¹ wherein T¹ together with a terminal nitrogen atom of R⁸ to which it is bound is an amine group or a functional derivative thereof;

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R⁷ is R¹ T¹ or is a group as hereinbefore defined for R⁶ T¹ wherein T¹ together with a terminal nitrogen atom of R⁶ to which it is bound is an amine group or a functional derivative thereof;

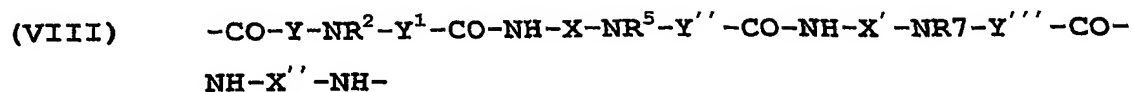
R⁵ is R¹ T¹ or a group as hereinbefore defined for R⁴ T¹ wherein T¹ together with a terminal nitrogen atom of R⁴ to which it is bound is an amine group or functional derivative thereof;

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R² is as hereinbefore defined for R¹ T¹; and

R³ is either

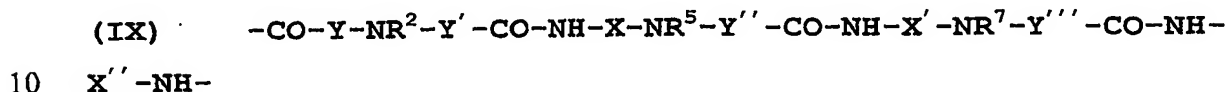
(a) p consecutive amidoamine moieties of formula VIII:



5 wherein:

p is a number of more than zero;

or (b) q consecutive amidoamine moieties of formula IX:

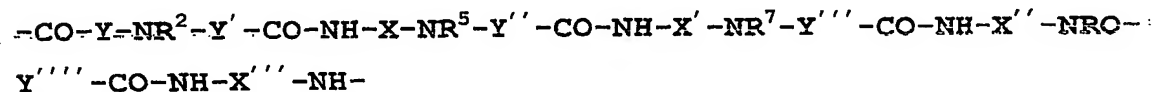


wherein:

q is a number greater than 0, or

(c) y consecutive amidoamine moieties of formula X:

15



(X)

20 wherein:

y is a number greater than 0.

15. A polymer according to claim 14, wherein $\text{R}^1 \text{ T}^1$ is the same as R^2 , or wherein $\text{R}^4 \text{ T}^1$ is the same as R^5 , or wherein R^6 is the same as R^7 , or wherein R^8 is the same as R^9 .

16. A polymer according to claim 14 or 15, wherein R^4 is option (a) and s is 0.

17. A polymer according to claim 14 or 15, in which R^4 is option (a) and s is 1.

18. A polymer according to claim 14 or 15, in which R^4 is

option (b) and R⁶ is option (a).

19. A polymer according to claim 14 or 15, in which R⁴ is option (b) and R⁶ is option (b).

5

20. A polymer according to any one of claims 14 to 19, in which n + p or m + q or x + y is in the range of from 1 to 20.

10 21. A polymer according to any one of claims 14 to 20, wherein each of Y, Y', Y'', Y''', Y'''', X, X', X'' and X''', which may be the same or different, is a cyclic hydrocarbon bridging group, an acyclic heteroatomic bridging group, a heterocyclic bridging group, or an
15 acyclic hydrocarbon bridging group, which itself may be optionally interrupted by or may terminate in one or more of a cyclic hydrocarbon group, an acyclic heteroatomic group, a heterocyclic group, or an amide group.

20 22. A polymer according to claim 21, wherein each of Y, Y', Y'', Y''', Y'''', X, X', X'' and X''', which may be the same or different, is a C₁₋₁₂ - alkylene or C₁₋₁₂ - alkenylene bridging group optionally interrupted by or
25 terminating in an oxygen atom, one, two or three optionally substituted nitrogen atoms, a cyclic hydrocarbon group, a heterocyclic group, or an amide group.

23. A polymer according to claim 22, wherein each of Y,
30 Y', Y'', Y''', Y'''', X, X', X'' and X''', which may be the same or different, is a C₁₋₆ - alkylene bridging group, or a C₁₋₄ - alkylene bridging group.

24. A polymer according to claim 23, wherein each of Y, Y', Y'', Y''', Y''', X, X', X'' and X''' is ethylene.

25. A polymer according to any one of claims 15 to 24, wherein T is selected from the group consisting of Cl, O-CO-R¹⁰, NHR¹², =NH, ≡N, H, OR¹¹ and OMet, wherein each of R¹⁰ and R¹¹, which may be the same or different, is hydrogen or an optionally substituted C₁₋₁₂-alkyl group; R¹² is hydrogen, an optionally substituted C₁₋₁₂-alkyl group, or NHR¹⁰ and Met is a metal.

26. A polyamidoamine according to claim 25, wherein T is a hydroxyl group.

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27. A polyamidoamine according to any one of claims 14 to 26, in which T¹ is selected from the group consisting of hydrogen and N - substituents rendering the nitrogen to which they are bound a functional derivative of an amine group.

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28. A polymer according to any one of claims 1 to 27, substantially as described in the Example.

29. An amidoamine polymer substantially as hereinbefore described.

30. A process for preparing a hyperbranched amidoamine polymer comprising:

(A) inducing polymeric condensation of a compound in which a nitrogen core is linked to:

a first amidoamine, (N - amidoamine) amidoamine, N - (N - amidoamine) amidoamine, or N-(N -(N - amidoamine)

amidoamine) amidoamine unit terminating in an amine group;

- 5 a second amidoamine, (N - amidoamine) amidoamine, N - (N - amidoamine) amidoamine, or N-(N-(N-amidoamine) amidoamine) amidoamine unit terminating in an amine group; and
- a third unit terminating in a carboxylic acid or related group.

10 31. A process according to claim 30, in which the nitrogen core is linked to:

- a first amidoamine, (N,N-diamidoamine) amidoamine, N,N-di(N,N-diamidoamine) amidoamine, or N,N-di(N,N-di N,N-diamidoamine) amidoamine) amidoamine unit terminating
- 15 in a amine group;

a second amidoamine, (N,N-diamidoamine) amidoamine, N,N-di(N,N-diamidoamine) amidoamine, or N,N-di (N,N-di (N,N-diamidoamine) amidoamine) amidoamine unit terminating in an amine group; and

- 20 a third unit terminating in a carboxylic acid or related group.

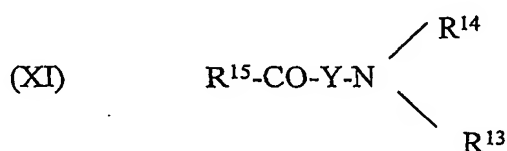
32. A process according to claim 30 or 31, wherein the terminal amine group is a primary amine group.

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33. A process according to any one of claims 30 to 32, wherein the related group of the carboxylic acid is selected from the group consisting of a salt, ester, anhydride, acide halide, acyl, amide, imide, nitrile,
- 30 aldehyde and hydrazide.

34. A process according to any one of claims 30 to 33, wherein the third unit terminates in a carboxylic acid group.

- 5 35. A process according to any one of claims 30 to 34, which comprises inducing polymeric condensation of a compound of formula:



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wherein:

Y is as hereinbefore defined;

R^{15} is as hereinbefore defined for group T;

Each of R^{13} and R^{14} , which may be the same or different, is
 15 a group $-Y'-CO-NH-X-NH_2$, $-Y'-CO-NH-X-NR^{16}(Y''-CO-NH-X'-NR^{17}R^{18})$ wherein R^{16} is hydrogen or $-Y'''-CO-NH-X'-NR^{17}R^{18}$,
 each of R^{17} and R^{18} , which may be the same or different, is
 hydrogen or $-Y''''-CO-NH-X''-NR^{19}R^{20}$ wherein each of R^{19} and
 R^{20} , which may be the same or different, is hydrogen or -
 20 $Y''''-CO-NH-X''-NH_2$, and
 $Y', X, X', X'', X''', Y'', Y'''$ and Y'''' are as hereinbefore
 defined.

36. A process according to claim 35, wherein R^{15} is
 25 hydroxyl.

37. A process according to claim 35 or 36, wherein R^{13}
 and R^{14} are both the group $-Y'-CO-NH-X-NH_2$, or

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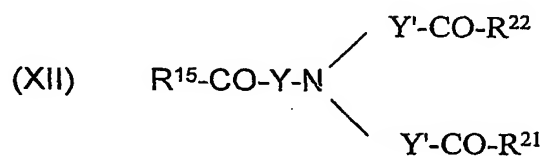
wherein R^{13} and R^{14} are both the group $-Y'-CO-NH-X-N-(Y''-CO-NH-X'-NH_2)_2$, or

wherein R^{13} and R^{14} are both the group $-Y'-CO-NH-X-N-(Y''-CO-NH-X'-N(Y'''-CO-NH-X''-NH_2)_2)_2$, or

wherein R_{13} and R_{14} are both the group $-Y'-CO-NH-X-N-(Y''-CO-NH-X'-N(Y'''-CO-NH-X''-N(Y''''-CO-NH-X'''-NH_2)_2)_2)_2$.

38. A process according to any one of claims 30 to 37, wherein step (A) is preceded by:
(A0) reacting a diamine of formula NH_2-X-NH_2 with a compound of formula:

15



wherein:
 R^{21} and R^{22} , which may be the same or different, are as hereinbefore defined for group T, and Y' , R^{15} and Y are as hereinbefore defined.

39. A process according to claim 38, wherein each of R^{21} and R^{22} is an OC_{1-6} -alkyl group.

40. A process according to claim 38 or 39, wherein step (A0) is preceded by:

(A00) reacting a compound of formula:

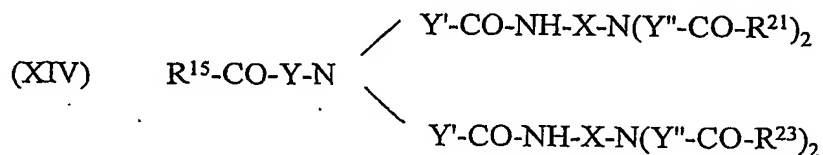


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wherein Y and R^{15} are as hereinbefore defined, with a Michael addition reagent.

41. A process according to any one of claims 30 to 37,
10 wherein step (A) is preceded by:

(A'O) reacting a diamine of formula $NH_2-X'-NH_2$ with a compound of formula:



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wherein:

R^{23} and R^{24} which may be the same or different, are as hereinbefore defined for group T and X, X' , Y, Y' and Y'' are as hereinbefore defined.

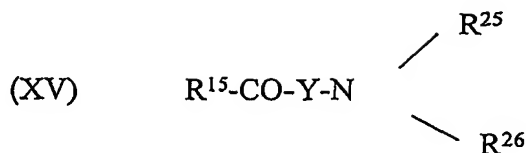
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42. A process according to claim 41, wherein each of R^{23} and R^{24} is an OC_{1-6} - alkyl group.

43. A process according to claim 41 or 42, wherein step
25 (A'O) is preceded by:

(A'OO) reacting a compound of formula:

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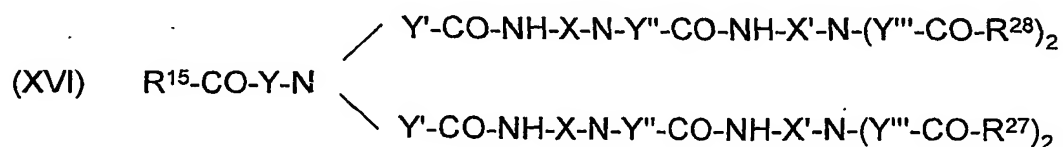


wherein Y and R¹⁵ are as hereinbefore defined; and each of
 5 R²⁵ and R²⁶, which may be the same or different, is a group
 -Y'-CO-NH-X-NH₂ wherein X and Y' are as hereinbefore
 defined, with a Michael addition reagent.

44. A process according to any one of claims 30 to 37,
 10 wherein step (A) is preceded by:

(A''0) reacting a diamine of formula NH₂-X''-NH₂ with a
 compound of formula:

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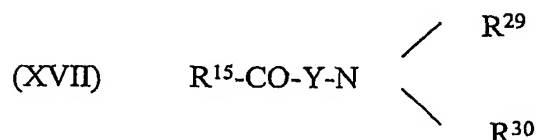
wherein R²⁷ and R²⁸, which may be the same or different,
 are as hereinbefore defined for group T, and X, X', X'',
 20 Y, Y', Y'' and Y''' are as hereinbefore defined.

45. A process according to claim 44, in which each of R²⁷
 and R²⁸ is an OC₁₋₆ alkyl group.

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46. A process according to claim 44 or 45, in which step (A''O) is preceded by:

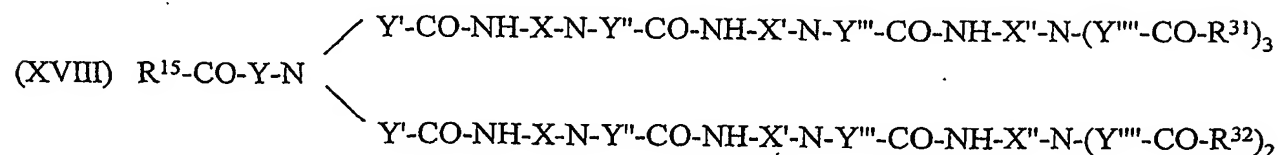
(A''OO) reacting a compound of formula:



wherein Y and R^{15} are as hereinbefore defined: and each of R^{29} and R^{30} , which may be the same or different, is a group $-Y'-CO-NH-X-N-Y''-CO-NH-X'-NH_2$ wherein X, X', Y' and Y'' are as hereinbefore defined, with a Michael addition reagent.

47. A process according to any one of claims 30 to 37, wherein step (A) is preceded by:

(A'''O) reacting a diamine of formula $NH_2-X'''-NH_2$ with a compound of formula:

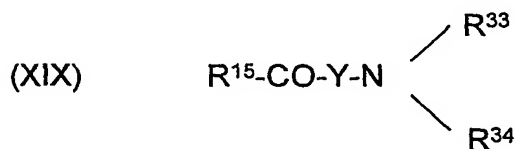


wherein R^{31} and R^{32} , which may be the same or different, are as hereinbefore defined for group T, and X, X', X'', X''', Y, Y', Y'', Y''' and Y'''' are as hereinbefore defined.

48. A process according to claim 47, wherein each of R^{31} and R^{32} is an OC_{1-6} -alkyl group.

49. A process according to claim 47 or 48, wherein step (A'''O) is preceded by:

(A'''OO) reacting a compound of formula:



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wherein Y and R¹⁵ are as hereinbefore defined; and each of R³³ and R³⁴ is a group-Y'-CO'NH-X-N-Y''-CO-NH-X'-N-Y'''-CO-NH-X''-NH₂ wherein X, X', X'', Y', Y'' and Y''' are as
10 hereinbefore defined, with a Michael addition reagent.

50. A process according to any one of claims 38 to 49, in which steps (AO), (A'O), (A''O) and (A'''O) are carried out at low temperature in a suitable solvent.

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51. A process according to any one of claims 40 to 49, wherein the Michael addition of steps (A'OO), (A''OO), (A'''OO) and (A''''OO) is carried out using an alkyl acrylate addition reagent.

20

52. A process according to any one of claims 30 to 51, wherein polymeric condensation is induced thermally, or by using an amide coupling agent.

25

53. A process according to claim 52, in which thermal condensation is carried out at a temperature in excess of 100°C at less than ambient pressure.

54. A process according to claim 52, in which polymeric condensation is carried out using an amide coupling agent selected from triphenylphosphite/pyridine, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate, or 4-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.

55. A process according to any one of claims 30 to 54, which further comprises the step of:

10 (B1) functionally derivatising the amine groups in which the first and second irregularly branched amidoamine units terminate.

56. A process according to any one of claims 30 to 55, which further comprises the step of:

(B2) functionally derivatising the carboxylic acid or related group in which the third irregularly branch amidoamine aiming unit terminates.

20 57. A process according to any one of claims 30 to 56 substantially as described in the Example.

58. A process for preparing a hyperbranched polymer substantially as hereinbefore described.

25

59. A composition comprising a hyperbranched amidoamine polymer together with an agent selected from the group consisting of a therapeutically or prophylactically active agent, an *in vivo* occurring or *in vitro* generated nucleotide, a diagnostic agent, a pesticide, a toxin, a protein, an antigen, a peptide, a nucleic acid, an amino acid and a bioactive agent.

30

60. A composition according to claim 59, wherein the nucleotide is a polynucleotide or oligonucleotide, a virus or a fragment thereof, an expression vector, gene
5 or fragment thereof, DNA, RNA, or wherein the diagnostic agent is a diagnostic contrast agent being or comprising a radionuclidic, paramagnetic, superparamagnetic, ferromagnetic, ferrimagnetic, antiferromagnetic, diamagnetic, fluorescent, phosphorescent, luminescent,
10 chemiluminescent, X-ray absorbent, UV absorbent, IR absorbent or ultrasound absorbent species, or wherein the protein is an immunoglobulin, an antibody, or a fragment thereof.
- 15 61. A composition according to claim 59 or 60, wherein the hyperbranched amidoamine polymer is coupled with, encapsulates, or is complexed or bound to, the agent.
- 20 62. A composition according to any one of claims 59 to 61, which is in the form of a solution, suspension, or emulsion.
- 25 63. A composition according to claim 62, wherein the solution, suspension or emulsion is an aqueous solution, suspension, or emulsion.
- 30 64. A composition according to any one of claims 59 to 63, which comprises a hyperbranched amidoamine polymer bound to a nucleotide or polynucleotide, a virus or fragment thereof, an expression vector, a gene or fragment thereof, DNA, or RNA.

65. A composition according to any one of claims 59 to 64, wherein the DNA or RNA is genomic DNA, mRNA, cDNA or aRNA.

5 66. A composition according to any one of claims 59 to 65 substantially as described in the Example.

67. A composition according to any one of claims 59 to 66 substantially as hereinbefore described.

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68. An *in vivo* transfection agent comprising an aqueous solution of a hyperbranched amidoamine polymer.

69. An *in vivo* transfection agent substantially as
15 hereinbefore described.

70. A hyperbranched amidoamine polymer or a composition thereof for use in therapy or prophylaxy.

20 71. A hyperbranched amidoamine polymer or composition thereof according to claim 70, wherein the hyperbranched amidoamine polymer is a polymer according to any one of claims 1 to 29.

25 72. A hyperbranched amidoamine polymer or composition according to claim 68 or 69, wherein the hyperbranched amidoamine polymer is used as a delivery agent for a therapeutically or prophylactically active agent.

30 73. A hyperbranched amidoamine polymer or composition thereof according to any one of claims 70 to 72, wherein the hyperbranched amidoamine polymer is used in gene therapy or prophylaxy.

74. A hyperbranched amidoamine polymer or composition thereof according to claim 73, wherein the hyperbranched amidoamine polymer is used as a nucleotide carrier, a
5 transfection agent or a vector.

75. A hyperbranched amidoamine polymer or composition thereof according to any one of claims 70 to 74 substantially as described in the Example.

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76. A hyperbranched amidoamine polymer or composition thereof according to any one of claims 70 to 75 substantially as hereinbefore described.

15 77. Use of a hyperbranched amidoamine polymer as a carrier, substrate or support.

78. Use according to claim 77, wherein the hyperbranched amidoamine polymer is used as a nucleotide carrier,
20 transfection agent or vector, or as a support or substrate, in combinatorial chemistry, catalysis, surface coating, implant coating or a photoactive system.

79. Use according to claim 77 or 78 substantially as
25 hereinbefore described.

80. Use of a hyperbranched amidoamine polymer in the preparation of a medicament for treating or preventing a genetically related condition or disorder.

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81. Use according to any one of claims 77 to 80, wherein the hyperbranched polyamidoamine is as claimed in any one of claims 1 to 29.

82. A hyperbranched polymer comprising amidoamine groups, wherein greater than 80% of the terminal groups are functional amine groups.

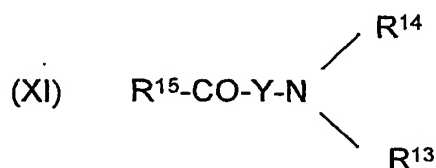
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83. A polymer according to claim 82, wherein the functionalised amine groups are protonated.

84. A hyperbranched polyamidoamine according to any one of claims 1 to 29, 82 and 83 prepared by a process according to any one of claims 30 to 58.

85. A composition comprising a hyperbranched polymer having less than 20% of methyl ester terminal groups, bound to a nucleotide or polynucleotide, a virus or fragment thereof, an expression vector, a gene or fragment thereof, DNA, or RNA.

86. A compound of formula:



wherein:

Y is as hereinbefore defined;

R¹⁵ as hereinbefore defined for group T;

Each of R¹³ and R¹⁴, which may be the same or different, is a group -Y'-CO-NH-X-NH₂-Y'-CO-NH-X-NR¹⁶-(Y''-CO-NH-X'-NR¹⁷R¹⁸), wherein R¹⁶ is hydrogen or -Y''-CO-NH-X'-NR¹⁷-R¹⁸; each of R¹⁷ and R¹⁸, which may be the same or different is hydrogen or -Y'''-CO-NH-X''-NR¹⁹-R²⁰, wherein each of R¹⁹ and

R^{20} , which may be the same or different, is hydrogen or $-Y''''-CO-NH-X'''-NH_2$; and
 Y' , X , X' , X'' , X''' , Y''' , Y'''' and Y'' are as hereinbefore defined.

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87. A compound according to claim 86, wherein R^{13} and R^{14} are both the group $-Y'-CO-NH-X-NH_2$, or

wherein R^{13} and R^{14} are both the group $-Y'-CO-NH-X-N-(Y''-CO-NH-X'-NH_2)_2$, or

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wherein R^{13} and R^{14} are both the group $-Y'-CO-NH-X-N-(Y''-CO-NH-X'-N(Y'''-CO-NH-X''-NH_2)_2)_2$, or

wherein R^{13} and R^{14} are both the group $-Y'-CO-NH-X-N-(Y''-CO-NH-X'-N(Y'''-CO-NH-X''-N(Y''''-CO-NH-X'''-NH_2)_2)_2)_2$.

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88. A compound according to claim 86 or 87 substantially as hereinbefore described.